Kunutsor, S. K., Mäkikallio, T. H., Voutilainen, A., Blom, A. W., Savonen, K., & Laukkanen, J. A. (2020). Cardiorespiratory fitness is not associated with fracture risk in middle-aged men. *European Journal of Clinical Investigation*, *50*(12), [e13360]. https://doi.org/10.1111/eci.13360

Research Letter

Cardiorespiratory fitness is not associated with fracture risk in middle-aged men

Short Title: Cardiorespiratory fitness and fractures

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Introduction

Fractures (particularly osteoporotic fractures) among the aging population constitute a substantial public health burden. They are a major cause of disability, morbidity, reduction in health-related quality of life, mortality and are associated with increased costs to healthcare systems.[1] The role of regular physical activity in the prevention of vascular disease, other chronic diseases and mortality is very well established.[2,3] Epidemiological data also suggests that physical activity is associated with reduced fracture risk.[4] Cardiorespiratory fitness (CRF) measured by maximal oxygen uptake (VO_{2max}), is the gold standard for assessing aerobic capacity and is an indicator of habitual physical activity.[5] Like physical activity, a wealth of epidemiologic evidence consistently shows CRF to be independently and inversely associated with adverse vascular outcomes, other chronic diseases and mortality.[5,6] One of the pathways by which physical activity reduces fracture risk is by increasing or maintaining bone mineral density (BMD).[7] A limited number of studies have reported increased levels of CRF to be associated with reduced risk for low BMD;[8,9] however, whether this translates to a reduced risk of fractures is uncertain. The association between objectively measured CRF and future risk of fractures is unknown. In this context, we sought to investigate the prospective association between objectively measured CRF and fracture risk in a general population of middle-aged Caucasian men.

Methods

Reporting of the study conforms to broad EQUATOR guidelines[10] and was conducted according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Supplementary Material** 1). The current

analysis employed the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a general population-based prospective cohort study that was set up to investigate risk factors primarily for cardiovascular disease (CVD) and other chronic diseases including osteoporotic fractures. The study design, recruitment methods, risk marker assessment and physical examinations have been described previously.[11] Briefly, the KIHD cohort comprised a representative sample of middle-aged men aged 42-61 years randomly recruited from a population register eastern Finland. The baseline cohort comprised of 2,682 eligible men who had baseline measurements performed between March 1984 and December 1989. In this analysis, complete information on CRF, relevant confounders, and fracture events was available for 2,173 men. The study research protocol was approved by the Research Ethics Committee of the University of Kuopio (December 1, 1983) and each participant gave written informed consent according to the Declaration of Helsinki. Maximal oxygen uptake was used as a measure of CRF and was estimated using a respiratory gas exchange analyzer during cycle ergometer exercise tests, which has been reported in detail previously.[5] As a result of aging, disease, lifestyle changes and measurement errors in exposure estimation in prospective cohort studies with long-term follow-up, analysis using only baseline measurements of an exposure could underestimate the true strength of any association between exposure and outcome (known as "regression dilution bias"[5]). To correct for this regression dilution bias, we used repeat measurements of VO_{2max} taken 11 years apart in a random subset of 560 men to estimate the regression dilution ratio (RDR). The outcome assessed was any fracture (defined as hip, humeral, or wrist fractures) that occurred from study entry to 2014. Data on incident fractures was collected from the National Hospital Discharge Register data (maintained by the Finnish Institute for Health and Welfare) by computer linkage using Finnish personal identification codes as well as a comprehensive review

of hospital records, discharge diagnoses, and inpatient physician claims. No losses to follow-up have so far been recorded. The events were coded by independent physicians according to the International Classification of Diseases Tenth Revision diagnostic codes for fractures by site. Cox proportional hazard regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were conducted using Stata version MP 16 (Stata Corp, College Station, Texas).

Results

The overall mean [standard deviation (SD)] age and CRF of study participants at baseline were 53 (5) years and 30.3 (8.0) mL/(kg.min) respectively (**Table 1**). The mean (SD) or CRF in the randomly selected sample who had repeat measurements 11 years after baseline was 27.6 (10.0) mL/(kg.min).

During a median (interquartile range) follow-up of 25.9 (18.1-27.9) years, a total of 113 fractures (annual rate 2.33/1,000 person-years at risk; 95% CI: 1.94 to 2.80) occurred. There were 68 hip fractures, representing an annual rate of 1.40/1,000 person-years at risk; 95% CI: 1.11 to 1.78. A restricted cubic spline curve of the association between CRF and fracture risk was potentially consistent with a linear shape (*p*-value for non-linearity=0.21) with a threshold value; the risk of fracture potentially decreased with increasing CRF from 6.4 to 27.4 mL/(kg.min), with no potential decrease in risk of fracture thereafter (**Figure 1**). The HR (95% CI) for fractures per 1 SD increase in CRF was 0.82 (0.66–1.01) on adjustment for age which was minimally attenuated on further adjustment for several established risk factors and other potential confounders (systolic blood pressure, prevalent coronary heart disease (CHD), smoking status, history of type 2 diabetes, total physical activity, socioeconomic status, alcohol

consumption, serum ionized calcium, and high sensitivity C-reactive protein) (**Table 2**). When the top tertile of CRF was compared to the bottom tertile, the corresponding adjusted HRs (95% CIs) were 0.78 (0.48–1.25) and 0.92 (0.55–1.53) respectively. The overall age-adjusted RDR of CRF was 0.58 (95% CI: 0.53-0.64), which suggests that if there was a significant association between CRF and fracture risk, using baseline measurements of CRF could under-estimate the risk by [(1/0.58)-1]*100 = 72%. The HRs were more extreme after correction for regression dilution bias (**Table 2**).

Discussion

Given existing evidence on the role of CRF in preventing chronic diseases and reducing the risk of low BMD,[5,8,9] we hypothesized that CRF may be linked to a reduced risk of fractures. In this first evaluation of the prospective association between objectively measured CRF and future risk of fractures in a middle-aged Caucasian male population, we found no significant evidence of an association. The annual incidence rate of hip fractures as at 2014 was 140.5/100,000 person-years, which is broadly in line with estimates reported by an analysis of a nationwide database within the period 1970-2016.[12] Kannus and colleagues[12] in analyses of the trend in the number and incidence of hip fracture in persons of 50 years and older demonstrated a decline in the incidence of hip fractures; the incidence in men was 256.5 per 100,000 persons in 1997 and fell to 194.7 in 2016.

Several important factors such as ageing, sex, heritability, physical activity, hormonal factors and nutrition are known to play a role in bone health and the development of fractures. Given that CRF is an objective marker of physical activity and may be used to define the relationship between physical activity and bone health, these null findings may seem unexpected.

Cardiorespiratory fitness is a modifiable risk factor that can be enhanced through regular aerobic physical activity. The level of CRF attained also depends on baseline health and fitness status of the individual, type, duration, and intensity of physical activity.[13] However, genetics and other environmental factors also play an important part in influencing CRF levels. It has been reported that about half of the variation in CRF is attributed to heritability, with the contribution of inherited factors to the response of CRF to physical activity accounting for approximating 45-50%.[13] Hence, our null findings may reflect differences between physical activity and CRF in the pathophysiology of fractures. Previous studies reporting a reduced risk of low BMD with CRF have mostly been based in relatively younger populations.[8,9] Whereas, studies conducted in middle-aged populations have demonstrated no evidence of an association between CRF and BMD.[14,15] Given that our study was based on a middle-aged population, the evidence suggests that it is unlikely that aerobic activity commenced during middle age will have an effect on BMD and subsequently fractures. Other reasons for the null findings could be related to study design factors and population characteristics such as (i) low statistical power due to the low fracture event rate; (ii) unmeasured confounding; and (iii) age, sex, or genetic background of the population. Finally, given the optimal CRF levels in our cohort which appeared to be maintained after 11 years of follow-up, there is a possibility that aerobic activity beyond a certain threshold may not have a beneficial effect on bone health. Indeed, in our assessment of the potential shape of the association between CRF and fracture risk assuming there was significant evidence of an association, the risk of fracture potentially decreased with increasing CRF from 6.4 to 27.4 mL/(kg.min), beyond which there was no further decrease. There is absence of previous investigations evaluating objectively measured CRF and fracture risk, hence further investigation

is required to assess the nature of any potential dose-relationship between CRF and fracture risk, especially in other populations and age groups.

The strengths of the present analysis include the new findings, the large-scale population-based representative sample, prospective cohort design and long-term follow-up, objectively measured CRF, and repeat measurements of CRF which allowed for quantification of regression dilution. Important limitations worthy of mention include the low event rate which also precluded evaluation of specific fracture sites, lack of generalisation of findings to women and other age groups, and lack of data on fractures related to falls or fall-related hospitalizations. We acknowledge the potential for selection bias given that study participants provided informed consent and this may potentially bias the results; however, this is an inherent limitation of observational cohort designs.

Conclusion

In summary, objectively measured CRF was not associated with future risk of fractures in a middle-aged general Caucasian population, suggesting that CRF may not play an important role in the pathogenesis of fractures in this population setting. Other large-scale studies are warranted to replicate or refute these findings.

Author Contributions

S.K.K.: Study design, data analysis and interpretation, drafting manuscript, and revising manuscript content and approving final version of manuscript; T.H.M: Study design and revising manuscript content and approving final version of manuscript; A.V.: Study conduct, responsibility for the patients and data collection, and revising manuscript content and approving final version of manuscript; A.W.B.: Study design and and revising manuscript content and approving final version of manuscript; K.S.: Study conduct, responsibility for the patients and data collection, and revising manuscript content and approving final version of manuscript; J.A.L.: Study design and conduct, responsibility for the patients and data collection, and revising manuscript content and approving final version of manuscript.

Acknowledgements

The authors thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, Finland for the data collection in the study.

J.A.L. acknowledges support from The Finnish Foundation for Cardiovascular Research, Helsinki, Finland. T.H.M. and S.K.K. acknowledge support from the Division of Cardiology, Department of Internal Medicine, Oulu University Hospital, Oulu, Finland via the Finnish Governmental Research Funding (VTR). S.K.K. is funded by the NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol. The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care. These sources had no role in design and conduct of the

study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

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References

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int.* 2006;17(12):1726-1733.

2. Colpani V, Baena CP, Jaspers L, et al. Lifestyle factors, cardiovascular disease and all-cause mortality in middle-aged and elderly women: a systematic review and meta-analysis. *Eur J Epidemiol.* 2018;33(9):831-845.

3. Kunutsor SK, Makikallio TH, Seidu S, et al. Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of prospective cohort studies. *Eur J Epidemiol.* 2020;35(5):431-442.

4. Rong K, Liu XY, Wu XH, et al. Increasing Level of Leisure Physical Activity Could Reduce the Risk of Hip Fracture in Older Women: A Dose-Response Meta-analysis of Prospective Cohort Studies. *Medicine (Baltimore).* 2016;95(11):e2984.

5. Laukkanen JA, Lavie CJ, Khan H, Kurl S, Kunutsor SK. Cardiorespiratory Fitness and the Risk of Serious Ventricular Arrhythmias: A Prospective Cohort Study. *Mayo Clin Proc.* 2019;94(5):833-841.

6. Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY, Rauramaa R. Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality: A Population-Based Follow-up Study. *Mayo Clin Proc.* 2016;91(9):1183-1188.

7. Heinonen A, Kannus P, Sievanen H, et al. Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. *Lancet.* 1996;348(9038):1343-1347.

8. DeFina LF, Leonard D, Willis BL, et al. High Cardiorespiratory Fitness Is Associated with Reduced Risk of Low Bone Density in Postmenopausal Women. *J Womens Health (Larchmt).* 2016;25(10):1073-1080.

9. Schwarz P, Jorgensen N, Nielsen B, Laursen AS, Linneberg A, Aadahl M. Muscle strength, power and cardiorespiratory fitness are associated with bone mineral density in men aged 31-60 years. *Scand J Public Health.* 2014;42(8):773-779.

10. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. *Eur J Clin Invest.* 2010;40(1):35-53.

11. Kunutsor SK, Whitehouse MR, Blom AW, Laukkanen JA. Low serum magnesium levels are associated with increased risk of fractures: a long-term prospective cohort study. *Eur J Epidemiol.* 2017;32(7):593-603.

12. Kannus P, Niemi S, Parkkari J, Sievanen H. Continuously declining incidence of hip fracture in Finland: Analysis of nationwide database in 1970-2016. *Arch Gerontol Geriatr.* 2018;77:64-67.

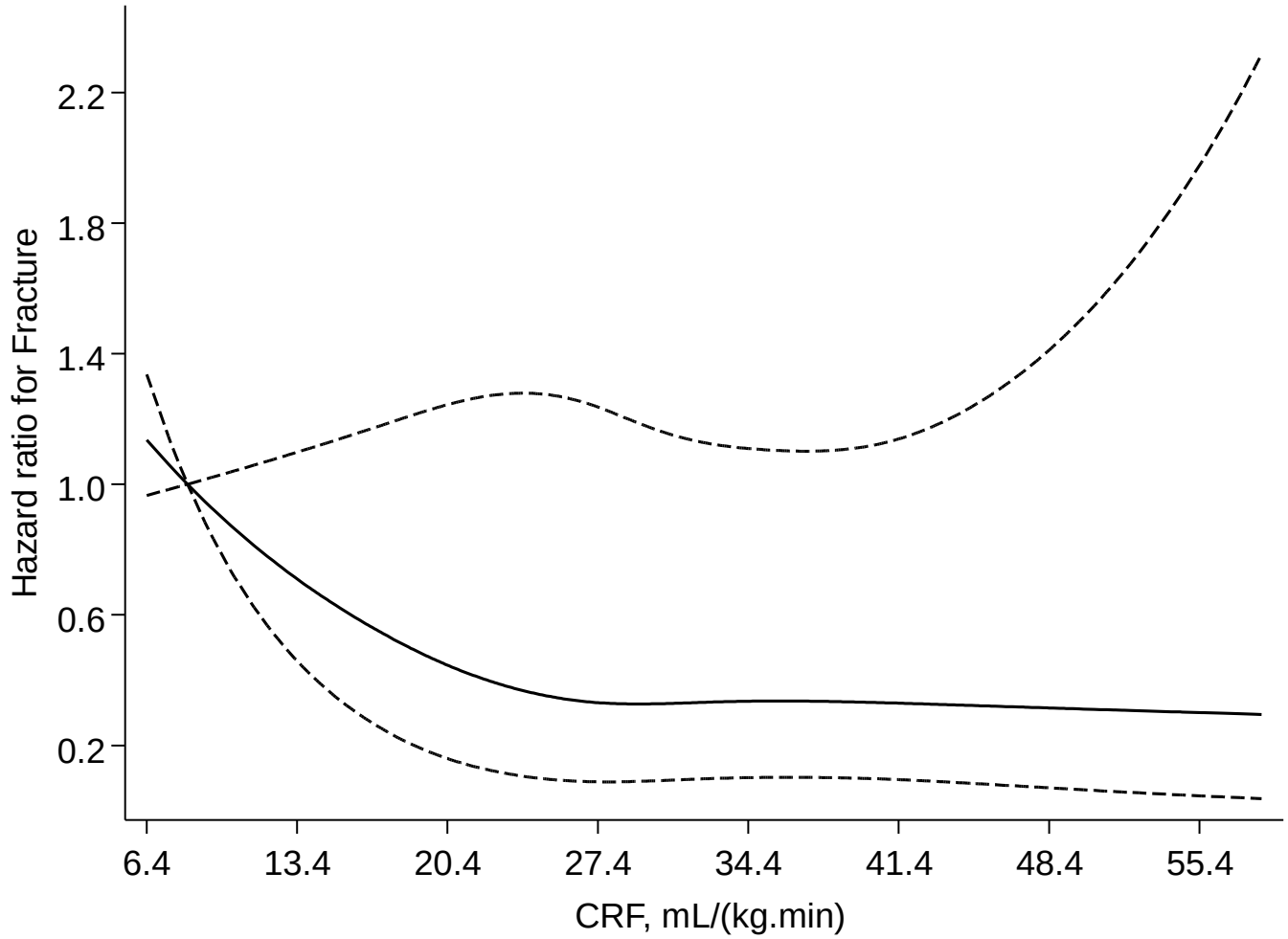
13. Laukkanen JA, Kujala UM. Low Cardiorespiratory Fitness Is a Risk Factor for Death: Exercise Intervention May Lower Mortality? *J Am Coll Cardiol.* 2018;72(19):2293-2296.

14. Huuskonen J, Vaisanen SB, Kroger H, et al. Determinants of bone mineral density in middle aged men: a population-based study. *Osteoporos Int.* 2000;11(8):702-708.

15. Huuskonen J, Vaisanen SB, Kroger H, Jurvelin JS, Alhava E, Rauramaa R. Regular physical exercise and bone mineral density: a four-year controlled randomized trial in middle-aged men. The DNASCO study. *Osteoporos Int.* 2001;12(5):349-355.

Figure title and legend

Figure 1. Restricted cubic spline of the hazard ratios of incident fracture with cardiorespiratory fitness



CRF, cardiorespiratory fitness

Table 1. Baseline participant characteristics

	Mean (SD), median (IQR), or n (%)
Baseline CRF, mL/(kg.min)	30.3 (8.0)
Repeat CRF at 11 years, mL/(kg.min)	27.6 (10.0)
Questionnaire/Prevalent conditions	
Age at survey (years)	53 (5)
Alcohol consumption (g/week)	32.0 (6.4-92.9)
Socioeconomic status	8.38 (4.24)
History of type 2 diabetes	73 (3.4)
Current smokers	689 (31.7)
History of CHD	515 (23.7)
History of hypertension	647 (29.8)
Physical measurements	
BMI (kg/m^2)	26.9 (3.5)
SBP (mmHg)	134 (17)
DBP (mmHg)	89 (10)
Total physical activity (kj/day)	1,213 (637-2,000)
Blood-based markers	
Total cholesterol (mmol/l)	5.90 (1.06)
HDL-C (mmol/l)	1.29 (0.30)
Fasting plasma glucose (mmol/l)	5.33 (1.21)
High sensitivity CRP (mg/l)	1.24 (0.69-2.37)
Serum ionized calcium (mmol/l)	1.18 (0.05)

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure

Table 2. Association between cardiorespiratory fitness and risk of fractures

CRF (mL/(kg.min))	Events/ Total	Model 1		Model 2	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline CRF					
Per 1 SD increase	113 / 2,173	0.82 (0.66 to 1.01)	0.06	0.88 (0.70 to 1.10)	0.27
T1 (6.36-26.86)	38 / 725	ref		ref	
T2 (26.87-33.24)	39 / 724	0.87 (0.55 to 1.36)	0.53	0.98 (0.62 to 1.57)	0.95
T3 (33.25-65.40)	36 / 724	0.78 (0.48 to 1.25)	0.30	0.92 (0.55 to 1.53)	0.74
Usual CRF*					
Per 1 SD increase	113 / 2,173	0.71 (0.49 to 1.02)	0.06	0.80 (0.54 to 1.19)	0.27
T1 (6.36-26.86)	38 / 725	ref		ref	
T2 (26.87-33.24)	39 / 724	0.78 (0.36 to 1.70)	0.53	0.97 (0.44 to 2.17)	0.95
T3 (33.25-65.40)	36 / 724	0.65 (0.28 to 1.48)	0.30	0.86 (0.36 to 2.08)	0.74

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; SD, standard deviation; T, tertile

*, indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")

Model 1: Adjusted for age

Model 2: Model 1 plus systolic blood pressure, prevalent coronary heart disease, smoking status, history of type 2 diabetes, total physical activity, socioeconomic status, alcohol consumption, serum ionized calcium, and high sensitivity C-reactive protein

Supplementary Material 1: STROBE 2007 Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Not applicable
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Methods
Study size	10	Explain how the study size was arrived at	Methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Methods

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods
		(b) Give reasons for non-participation at each stage	Methods
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Table 1
		(*b*) Report category boundaries when continuous variables were categorized	Results; Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results; Figure 1
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 8